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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,839	03/23/2001	Michael S.C. Fung	TNX00-04	6910
26839	7590	06/04/2004	EXAMINER	
TANOX, INC. 10301 STELLA LINK HOUSTON, TX 77025			VANDERVEGT, FRANCOIS P	
			ART UNIT	PAPER NUMBER
			1644	

DATE MAILED: 06/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/816,839

Applicant(s)

FUNG ET AL.

Examiner

F. Pierre VanderVegt

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 March 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 19,20,22-30 and 32-37 is/are pending in the application.
- 4a) Of the above claim(s) 28-30 and 32-35 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 19,20,22-27,36 and 37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

This application claims priority to provisional application 60/191,429.

Claims 1-18, 21 and 31 have been canceled.

New claims 36 and 37 have been added.

Claims 19, 20, 22-30 and 32-37 are currently pending.

Claims 28-30 and 32-35 stand withdrawn as being drawn to a non-elected invention.

Claims 19, 20, 22-27 and 36-37 are the subject of examination in the present Office Action.

1. **The following grounds of rejection have been maintained.**

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 19, 20, 23 27 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Anderson et al. (Biochem. Soc. Trans. 1987, 15(4):660-661)(IDS; of record).

It was previously stated: "Anderson et al teaches a monoclonal antibody produced by a hybridoma cell line, which binds to C2a or to the C2a portion of C2 that inhibits the classical pathway (page 660; paragraph bridging columns in particular) and a pharmaceutical composition comprising same with an acceptable carrier (in phosphate-buffered saline; Fig. 1 in particular)[claim 27]. Applicant has amended claims 19 and 20 to recite the limitation that the antibody "inhibits" complement activation "at a molar ratio of 1:2 (antibody to C2)." Applicant asserts in the reply filed March 13, 2003 that the antibody taught by Anderson "requires a 7 fold molar excess of antibody to C2 in order to achieve a 50% inhibition of C2 hemolytic activity" and that "[f]igure 3 illustrates that the present invention antibodies are capable of inhibiting the classical pathway at a molar ratio of 1:2," concluding, "[t]herefore, the present claims are not anticipated by the Anderson reference." It is acknowledged that the degree of complement inhibition by the Anderson antibody may not be as high as the inhibition by 175-62 of the present invention, the only antibody for which "molar" data is given. However, the claims are drawn to "inhibition" at the 1:2 ratio, not ablation. It is respectfully submitted that the threshold for "inhibition" is low, the accepted meaning of the word in biological terms as a decrease, limit, or block of the action or function of a target. Accordingly, in order to satisfy the metes and bounds of the claims, the Anderson antibody only has to decrease complement activation when incubated with C2 at a ratio of 1:2. The term does not require a complete ablation of complement activation. Accordingly, while Anderson does not specifically state that the antibody can cause a decrease in complement activation when at a antibody:C2 ratio of 1:2, silence about a particular property does not necessarily constitute the absence of said property. There is equally no showing that the antibody of Anderson does not inhibit at the recited ratio and no side-by-side comparison to show that the instantly disclosed antibodies possess properties not found in the prior art

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antibody. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the materials, i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is on the Applicant to prove that the claimed materials are different from those taught by the prior art and to establish patentable differences. See *In re Best* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989)."

Applicant's arguments filed March 4, 2004 have been fully considered but they are not persuasive. Applicant has amended the claims to recite that the anti-C2a antibody inhibits complement activation more than 50% at a molar ratio of 1:2 (antibody to C2). Applicant argues that this limitation differentiates the claimed antibody from the antibody of Anderson because the antibody of Anderson "is incapable of this level of inhibition at a ratio of 1:2, since at a seven fold molar excess the antibody was only able to achieve a 50% inhibition. The Examiner respectfully disagrees with Applicant's position. Anderson teaches that the inhibition assay was run under published conditions known in the art (Kerr, 1981 cited in Anderson of record). Applicant's disclosure of an antibody with the property of antibody capable of inhibiting complement activation more than 50% at a molar ratio of 1:2 is limited to a single species, the mAb 175-62, as shown in Figure 3. It is further notable that the mAb 175-62 only inhibits CP hemolysis in the assay when the serum concentration in the buffer/medium is greater than 10%. At serum concentrations of less than 10%, the inhibitory ability of mAb 175-62 is greatly reduced. Accordingly, the activity of the antibody disclosed by Anderson and the 175-62 mAb of the instant disclosure have not been compared under equivalent conditions. It is important to note that the claims at hand are not limited to mAb 175-62 or to antibodies that inhibit complement activation under equivalent conditions but encompass ANY antibody with the properties recited in the claim. It is possible that the antibody taught Anderson inhibits complement activation more than 50% at a molar ratio of 1:2 (antibody to C2) when tested under the instantly disclosed conditions comprising greater than 10% serum in the medium/buffer. Therefore, it must be reiterated that the office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the materials, i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. Accordingly, without regard to the issues addressed *infra* under 35 USC § 112, in order to establish that there is a difference between the materials, Applicant must provide evidence to that effect, such as a demonstration that the antibody of Anderson does not inhibit complement activation more than 50% at a molar ratio of 1:2 (antibody to C2) when tested under the instantly disclosed conditions comprising greater than 10% serum in the medium/buffer.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 19 and 24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (Biochem. Soc. Trans. 1987, 15(4):660-661; of record) in view of Janeway et al, Immunobiology, 3rd edition, Current Biology Ltd, London, England 1997 pages 13:7-8; of record), Vakeva et al. (Circulation. [1998] 97(22):2259-2267; U on form PTO-892, newly cited) and Stoltzner et al (Am J Pathol. [2000]156(2):489-499; V on form PTO-892, newly cited).

It was previously stated: "Anderson has been discussed supra.

Anderson does not teach a humanized form of the antibody as recited in claim 7.

Janeway teaches standard techniques in the art at the time the invention was made including that humanized antibodies comprise the CDRs of a mouse monoclonal antibody onto the human framework of a human immunoglobulin, and that said chimeric antibodies are far less immunogenic in humans than the parent mouse monoclonal antibodies, and thus they can be used for treatment of humans with far less risk of anaphylaxis than the parent non-human monoclonal antibodies. For similar purposes, monoclonal antibodies that are entirely human in origin can be made in mice lacking endogenous immunoglobulin genes.

Vakeva teaches that "[s]everal lines of investigation support a role for complement in the pathogenesis of [myocardial infarction/reperfusion] injury" (page 2259, first column in particular). Vakeva teaches that treatment of rats with an anti-C5 antibody "significantly inhibits cell apoptosis, necrosis and [peripheral mononuclear cell] infiltration in the rat despite C3 deposition" (Abstract in particular). C5 is known in the art to be a "late" component in the complement cascade and C3 is similarly known to be an "early" or "middle" component.

Stoltzner teaches that the complement system mediates the inflammatory response activated in Alzheimer's disease (AD; Abstract in particular). Stoltzner teaches that AD amyloid plaques in Down's syndrome patients comprise, among other complement components, the classical pathway proteins C1q (early) and C3 (middle) (see entire document). Stoltzner teaches that "therapeutic interventions aimed at slowing or halting this cascade of inflammation in response to compacted [amyloid-beta protein] in the brain may be of value in treating or preventing AD" (page 498, last sentence in particular).

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It would have been *prima facie* obvious to a person having ordinary skill in the art at the time the invention was made to combine the teachings of Janeway regarding chimeric and/or humanized forms of antibodies with the anti-C2 monoclonal antibodies taught by Anderson because Janeway et al teaches that humanized antibodies are far less immunogenic in humans and have far less risk of anaphylaxis and because the antibody taught by Anderson et al. binds to C2a or to the C2a portion of C2, and inhibits the classical pathway. One would have been motivated to combine the teachings with a reasonable expectation of success by the teaching of Vakeva that anti-complement antibodies are effective in reducing complement-mediated damage of tissue and the teachings of Stoltzner that early complement proteins also have a damaging effect in inflammation and that it is desirous to interfere with the classical cascade at an earlier, rather than a later, stage. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary."

Applicant asserts that the rejection fails based upon the perceived shortcomings of the Anderson reference in light of the amendment to the claims. Applicant has offered no further arguments regarding the ground of rejection. Accordingly, the ground of rejection is maintained in light of the further comments in paragraph 2, *supra*.

4. Claims 19 and 22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (Biochem. Soc. Trans. 1987, 15(4):660-661; of record) in view of U.S. Patent No. 5,861,156 to George et al. (of record), Vakeva et al. (Circulation. [1998] 97(22):2259-2267; U on form PTO-892, newly cited) and Stoltzner et al (Am J Pathol. [2000]156(2):489-499; V on form PTO-892, newly cited).

It was previously stated: "Anderson has been discussed *supra*.

Anderson does not teach fragments of the antibody as recited in claim 22.

The '156 patent teaches in Column 10, lines 42-62, that the complete antigen binding site of an antibody may be obtained by recombinant methods from monoclonal antibodies or combinatorial libraries, and may correspond to the two-chain 50 kD Fab or related Fab' fragments, the two-chain 25 kD Fv fragment, or the 26-27 kD single-chain Fv. '156 teaches that all of these species are smaller and far more rapid in biodistribution than IgG monomers or dimers and that their reduced size is advantageous for primary targeting.

Vakeva teaches that "[s]everal lines of investigation support a role for complement in the pathogenesis of [myocardial infarction/reperfusion] injury" (page 2259, first column in particular). Vakeva teaches that treatment of rats with an anti-C5 antibody "significantly inhibits cell apoptosis, necrosis and [peripheral mononuclear cell] infiltration in the rat despite C3 deposition" (Abstract in particular). C5 is known in the art to be a "late" component in the complement cascade and C3 is similarly known to be an "early" or "middle" component.

Stoltzner teaches that the complement system mediates the inflammatory response activated in Alzheimer's disease (AD; Abstract in particular). Stoltzner teaches that AD amyloid plaques in Down's syndrome patients comprise, among other complement components, the classical pathway proteins C1q (early) and C3 (middle) (see entire document). Stoltzner teaches that "therapeutic interventions aimed at slowing or halting this cascade of inflammation in response to compacted [amyloid-beta protein] in the brain may be of value in treating or preventing AD" (page 498, last sentence in particular).

It would have been *prima facie* obvious to a person having ordinary skill in the art at the time the invention was made to combine the teachings of the '156 patent regarding Fab, F(ab)₂, Fv or ScFv forms of antibodies with the anti-C2 monoclonal antibodies taught by Anderson because the '156 patent teaches

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that antibody fragments are smaller and far more rapid in biodistribution than IgG monomers or dimers and that their reduced size is advantageous for primary targeting, and because the antibody taught by Anderson binds to C2a or to the C2a portion of C2, and inhibits the classical pathway. One would have been motivated to combine the teachings with a reasonable expectation of success by the teaching of Vakeva that anti-complement antibodies are effective in reducing complement-mediated damage of tissue and the teachings of Stoltzner that early complement proteins also have a damaging effect in inflammation and that it is desirous to interfere with the classical cascade at an earlier, rather than a later, stage. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary."

Applicant asserts that the rejection fails based upon the perceived shortcomings of the Anderson reference in light of the amendment to the claims. Applicant has offered no further arguments regarding the ground of rejection. Accordingly, the ground of rejection is maintained in light of the further comments in paragraph 2, *supra*.

5. **The following new grounds of rejection have been necessitated by Applicant's amendment.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 19, 20 22-24, 27 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the monoclonal antibody 175-62, does not reasonably provide enablement for the genus of antibodies that inhibit complement activation more than 50% at a molar ratio of 1:2 (antibody to C2). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicant has amended the claims to recite that the anti-C2a antibody inhibits complement activation more than 50% at a molar ratio of 1:2 (antibody to C2). Applicant argues that the amendment is supported by the demonstration of "numerous examples of antibodies that significantly inhibit C2 mediated complement activation, all of which inhibit complement activation more than 50% (Figure 2). While it is acknowledged that Figure 2 discloses several mAbs capable of greater than 50% complement inhibition at suitable concentration, the claim specifically requires that the antibodies inhibits complement activation more than 50% at a molar ratio of 1:2. This molar ratio of mAb to C2a is not shown for the

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antibodies in Figure 2. The limitation of inhibiting complement activation more than 50% at a molar ratio of 1:2 is shown only for a single monoclonal antibody, mAb 175-62, in Figure 3. It is further notable that the mAb 175-62 only inhibits CP hemolysis in the assay when the serum concentration in the buffer/medium is greater than 10%. At serum concentrations of less than 10%, the inhibitory ability of mAb 175-62 is greatly reduced. Accordingly, the only antibody disclosed as having the claimed properties may not have those properties itself, dependent upon the conditions under which the assay is performed. Based upon the limited disclosure of a single species, the artisan would not be able to predict other antibodies that satisfy the metes and bounds of the claim or the conditions under which the limitations must be satisfied. It would require an undue amount of experimentation on the part of the artisan to make antibodies that satisfies the breadth of the claimed genus or to determine the conditions under which any particular antibody might satisfy the claimed limitations.

In view of the breadth of the claims, the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, it would take undue trials and errors to practice the claimed invention and this is not sanctioned by the statute.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 25, 26 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a monoclonal antibody made by a hybridoma cell deposited with the ATCC. However, the claims recite that the antibody itself is deposited. The ATCC does not accept deposits of particular antibody molecules, only of the viable hybridoma cell line that makes the antibody. Applicant should amend the claim to more clearly convey the antibody is made by the deposited hybridoma, not that the hybridoma makes a deposited antibody.

Request for Rejoinder

8. Applicant's request for rejoinder with reference to MPEP 821.04 is acknowledged. However, as the product claims have not been found to be allowable in the present Office Action, the withdrawn claims to methods of using the product are not being rejoined and stand as withdrawn.

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Conclusion

9. No claim is allowed.


10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

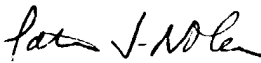
A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00; Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

F. Pierre VanderVegt, Ph.D. 
Patent Examiner
November 26, 2003


PATRICK J. NOLAN, PH.D.
PRIMARY EXAMINER